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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/004,219 | 11/02/2001 | Johannes Maria Franciscus Gerardus Aerts | 2183-5136US | 6939 |

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TRASK, BRITT & ROSSA
P.O. Box 2550
Salt Lake City, UT 84110

| EXAMINER |
|---|
| RAO, MANJUNATH N |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1652 | 16 |

DATE MAILED: 08/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/004,219 | AERTS ET AL. | |
| | Examiner | Art Unit | |
| | Manjunath N. Rao, Ph.D. | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) *10-14,22-32,35-37 and 42-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,15-21,33,34 and 38-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

Claims 1-44 are currently pending in this application. Claims 1-9, 15-21, 33-34, 38-41 are now under consideration. Claims 10-14, 22-32, 35-37, 42-44 remain withdrawn from consideration as being drawn to non-elected invention.

### *Election/Restrictions*

Applicant's election without traverse of Group I, claims in Paper No. 1-9, 15-21, 33-34, 38-41 is acknowledged.

### *Drawings*

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

### *Information Disclosure Statement*

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

***Specification***

The amendment filed 6-3-02 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Paper copy of the sequences filed on the above date indicate a total number of sequences as 14. However, perusing through the originally filed specification including the figures, Examiner could account for only 11 sequences. Furthermore, it is not clear to the Examiner as which sequence filed in the original specification corresponds to which specific SEQ ID NO in the listing filed on the above date. Therefore, Examiner considers the three additional sequences filed as new matter. Applicants have amended the specification twice. Applicants have not provided any explanation regarding the SEQ ID NO in the new sequence listing. Examiner urges applicants to provide a detailed list of originally filed sequences along with references to their page numbers where they occur in the original specification and their corresponding SEQ ID NO in the new sequence listing filed on the above date. Until the ambiguities of the total number of sequences and their recitations in the original specification are resolved, Examiner considers the sequences filed on the above date as new matter. Applicant is required to cancel the new matter in the reply to this Office Action.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4 and claims 5-9, 15-21, 33-34, 38-41 all of which depend from claim 3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 4 recites that the mucinase of claim 3 is encoded by a nucleotide sequence corresponding to the nucleotide sequence as shown in figure 8. However, figure 8 depicts only amino acid sequences but not nucleotide sequence. Therefore it is not clear to the Examiner as to whether applicants are claiming a nucleic acid sequence or an amino acid sequence. Furthermore, applicants do not provide SEQ ID NO in claims referring to sequences. Without knowing what sequences applicants are claiming, it would be impossible for the Examiner to do a thorough search. Therefore, applicants are urged to provide specific SEQ ID NO in the claims.

Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 5 recites the phrase "an effective amount of the mucinase". The metes and bounds of the above phrase is not clear to the Examiner. It is clear to the Examiner that applicants are claiming a pharmaceutical composition comprising the mucinase, but the effective amount is against what, is the question rendering the claim indefinite. Correction is required.

Claims 33-34 and 38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 33-34 and 38 recite the phrase "derived from the amino acid sequence shown in figure 8". The metes and bounds of this phrase is not clear to the Examiner. Literally, while the term "derived" means "to isolate from or obtain from a source", the above term could also mean "to arrive at by reasoning i.e., to deduce or infer" or also mean "to produce or obtain from another substance". Therefore, it is not clear to the Examiner either from the specification or from the claims as to what applicants mean by the above phrase. It is not clear to the Examiner whether the "derived from the amino acid sequence shown in figure 8" encompasses a single specific sequence in figure 8 and if so which specific sequence or whether it encompasses recombinants, variants and mutants of any mucinase from any other source and labeled as "derived from the amino acid sequence shown in figure 8". As applicants have not provided a definition for the above phrase, Examiner has interpreted the claims broadly to mean, that a peptide of at least about 8 amino acids "derived from the amino acid sequence shown in figure 8" encompasses peptide sequences which are recombinants, variants, or mutants of any mucinase/chitinase. Examiner has given the same interpretation while considering the claims for all other rejections.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 15-21, 33-34, 38 and 41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mucinase comprising two amino acid sequences depicted in figure 8 (i.e., SEQ ID NO:9 or 14) isolated from either mouse or humans respectively or pharmaceutical composition comprising the same, does not reasonably provide enablement for any mammalian mucinase isolated from any or all mammals or any or all mucinases isolated from any or all of its sources including mutants variants and recombinants or any pharmaceutical composition comprising the same. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-9, 15-21, 33-34, 38 and 41 are so broad as to encompass any mammalian mucinase or any or all mucinases from any source including recombinants mutants and variants of SEQ ID NO:9 and 14. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of mucinases broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard

to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only two mucinases. It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides with an undefined function/activity. The specification is limited to teaching the use of SEQ ID NO: 9 and 14 as a mucinase but provides no guidance with regard to the making of variants and mutants or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any mucinase or variants of SEQ ID NOS:9 and 14 because the specification does not establish: (A) regions of the protein structure which may be modified without affecting mucinase activity; (B) the general tolerance of mucinases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of any mucinase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including mucinases from all sources and mucinases with an enormous number of amino acid modifications to SEQ ID NOS: 9 and 14. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of mucinase genes having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 1-9, 15-21, 33-34, 38 and 41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-9, 15-21, 33-34, 38 and 41 are directed to polypeptides with mucinase activity including variants of SEQ ID NO:9 and 14 (mucinases of figure 8). Claims 1-9, 15-21, 33-34, 38 and 41 are rejected under this section of 35 USC 112 because the claims are directed to a genus of polypeptides derived from SEQ ID NO:9 or 14 including modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution of an amino acid residue in SEQ ID NO:9 or 14 and fragments of same that have not been disclosed in the specification. No description has been provided of the modified polypeptide sequences encompassed by the claim. No information, beyond the characterization of SEQ ID NO:9 and 14 has been provided by applicants which would indicate that they had possession of the claimed genus of modified polypeptides. The specification does not contain any disclosure of the structure of all the polypeptide sequences derived from SEQ ID NO:9 and 14, including fragments and variants within the scope of the claimed genus or the genus of polypeptides claimed. The genus of polypeptides claimed is a large variable genus including peptides which can have a wide variety of structure. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only two species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 8, 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Smith et al. (Mol. Microbiol., 1994, Vol.13(1):153-160). This rejection is based upon the public availability of a printed publication. Claims 1-4, 8, 18 of the instant application is drawn to a recombinant or purified mammalian mucinase or a modified form of the same having mucin hydrolyzing activity, isolated from a host cell producing the same and encoded by a nucleic acid sequence and a composition comprising the same. Smith et al. disclose a recombinant mucinase encoded by a polynucleotide which encodes said enzyme from a host cell and a composition with a carrier comprising said enzyme. Examiner is aware that the mucinase in the reference is not a mammalian mucinase. However, claim 1 is also drawn to modified for of any mammalian mucinase as well. Since there is no limitation placed on the number of changes that can be present in the modified mammalian mucinase, claims 1-4, 8 and 18 read on the mucinase disclosed by Smith et al. Thus Smith et al. anticipate claims 1-4, 8 and 18 of this application as written.

Claims 1-4, 8, 15, 18, 33-34 are rejected under 35 U.S.C. 102(a) as being anticipated by Boot et al. (J. Biol. Chem., March 2001, Vol. 276(9):6770-6778). This rejection is based upon

the public availability of a printed publication. Claims 1-4, 8, 18, 33-34 of the instant application is drawn to a recombinant or purified mammalian mucinase or a modified form of the same having mucin hydrolyzing activity and further comprising chitin hydrolyzing activity, isolated from a host cell producing the same and encoded by a nucleic acid sequence and a composition comprising the same and a peptide of at least 8 amino acids which mimicks the mucinase epitope or having antigenicity. Boot et al. disclose a recombinant enzyme encoded by a polynucleotide which encodes said enzyme from a host cell and a composition with a carrier comprising said enzyme. The enzyme disclosed by Boot et al. has 100% amino acid sequence identity with SEQ ID NO:9 and 14 which applicants claim as a mucinase (see enclosed sequence alignments). Examiner is aware that the reference does not disclose the polypeptide as having mucinase activity. However as the amino acid sequences are 100% identical Examiner takes the position that mucinase activity is inherent to said polypeptide and therefore, the above reference anticipates claims 1-4, 8, 15, 18, 33-34. Thus Boot et al. anticipate claims 1-4, 8, 15,18, 33-34 of this application as written.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5-7, 9, 16-17, 19-21, 33-34, 38 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al. or Boot et al. as applied to claims 1-4, 8, 15 and 18 above, and further in view of Sajjan et al. (J. Clin. Invest., 1992, Vol. 89(2):648-656).

The references of Boot et al. and Smith et al. as it applies to claims 1-4, 8, 15 and 18 has been discussed above.

Sajjan et al. teach that although not as prevalent as Ps.aeruginosa, Ps.cepacia is another opportunistic pathogen which colonizes the lungs of some patients with cystic fibrosis which leads to a syndrome called as "cepacia syndrome". The above reference also teaches that Ps.cepacia is capable of causing this syndrome because of its ability to bind to mucins secreted by such patients and thrive in the mucus of said patients.

Therefore, combining the teachings of Boot et al. or Smith et al. which teach enzymes capable of degrading mucins, and the teachings of Sajjan et al. which teaches that the cepacia syndrome, an additional complication which cystic fibrosis patients face, it would have been obvious to those skilled in the art to make pharmaceutical composition comprising said enzyme, or pharmaceutical compositions comprising additional enzymes such as a DnaseI, in order to treat or as a prophylactic agent for cepacia syndrome. One of ordinary skill in the art would have been motivated to do so as Boot et al. and Smith et al. provide a mucinase capable of degrading mucin and Sajjan et al. teach the role of mucin in cepacia syndrome. One of ordinary skill in the would have a reasonable expectation of success because Boot et al. and Smith et al. provide the enzyme in the recombinant or purified form ready for use and Sajjan et al. teach the role of mucins in cepacia syndrome.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

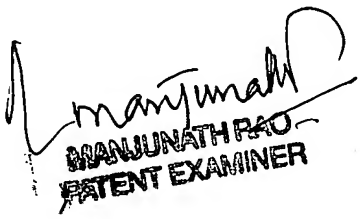
This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

***Conclusion***

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath Rao whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 7:30 a.m. to 4:00 p.m. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.




Manjunath N. Rao Ph.D.
Patent Examiner, A.U. 1652
8/23/03